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Antimicrobial Resistance, Livestock and the Environment

This is a report from a workshop on antimicrobial resistance (AMR), livestock and the environment, held on May 31st 2016 at 50 George Square, Edinburgh, funded by the Natural Environment Research Council and the University of Edinburgh. The focus of this workshop was the relationship between environment and livestock in the context of antimicrobial resistance. In particular, the aim was to examine processes in water, soil and plants, while retaining an understanding of what is practical to undertake in farm conditions.

The specific objectives of the meeting were to:

- Co-produce practice-oriented research needs
- Progress towards sustainable livestock production by better sharing of knowledge
- Promote a constructive dialogue between different sectors in research and industry
- Raise awareness of current state of knowledge
- Identify synergies and opportunities for deeper co-operation across disciplines and stakeholders

The multi-stakeholder perspective generated considerable productive interaction which highlighted the many knowledge gaps and the complex environments to be considered. No one single discipline or stakeholder understood the breadth of both science and practice within the sphere of action being considered. This report identifies the key research needs identified by this unique gathering of participants (see Annex 3 for attendees).

Key findings included:

- i) Much better understanding of the sources, dynamics and flows of AMR on farms, and their environments are needed. The role of biocides and metals in AMR development may have been under-recognised and raises issues around the use of these materials for biosecurity.
- ii) A more systematic approach is needed to better understand the relationships and trade-offs between reduced antibiotic use in livestock, human health, economic viability of farms, food security and safety, international trade and ecosystem resilience.

- iii) Rapid diagnostic devices could have a major role in more discriminating use of antibiotics, but they have proved to be difficult to develop.
- iv) Evidence needs to be provided to farmers, and their networks, that reducing antibiotic resistance will result in reduction of AMR.
- v) Provision of standardised, open access data relating to AMR, both on an individual farm basis, and internationally, would greatly assist research.
- vi) Opportunities may exist for industry action to reduce or eradicate immune modulating diseases such as BVD or PRRs to reduce use of antibiotics.

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1. BRIEF SUMMARY OF PRESENTATIONS

Grace Webster

Grace is a pig veterinarian and she emphasised three potential management practices: use of penside diagnostics, management factors and improving biosecurity. Specific issues raised in discussion following this presentation can be found in Annex 2.

Andrew Singer

Andrew comes from an environmental science perspective with particular emphasis on the role of biocides and metals in antibiotic resistance. A brief summary of Andrew's presentation can be found in Annex 1.

In *Discussion* the issue of identifying appropriate threshold levels for biocides and metals was discussed, as was the possibility of recycling metals e.g. as ash.

Elizabeth Wellington

Elizabeth also comes from an environmental science perspective and emphasised the interactions between manure and soil. She argued that most AMR problems in the environment come from manure, both human and animal. The interactions in soil and among soil organisms is complex and there are many research needs in this area.

Derek Armstrong

Derek gave a livestock industry perspective and emphasised that economics is a very important consideration for antibiotic use in agriculture, as management tends to be better when farmers have money. He recognised that there is a debate as to the extent to which antibiotics are used to treat bacterial infections or to compensate for poor environment. Research questions raised by Derek can be found in Annex 2.

2. SUMMARY OF CO-PRODUCED RESEARCH NEEDS HIGHLIGHTED IN DISCUSSION

In plenary session, participants were asked to identify research questions important to resolving issues of AMR in the environment. These questions were then clustered so that each breakout group could tackle a generally defined issue by going into more depth on key research needs, drawing on the mixture of perspectives present in each breakout group. While clusters can be 'sliced' in different ways, the five below depict critical research needs identified by this group.

a) Sources of AMR - Much more knowledge is needed about sources enabling AMR development and transmission.

b) Mitigation methods – Improved knowledge is needed on how to bring about behavioural change and ensure action at an individual farm and global level; how communication across sectors could be improved; and what technologies might minimise spread of AMR in the medium term?

c) Underlying scientific questions - A wide range of questions need research from multiple disciplines, from the genetics and evolution of AMR, to environmental and manure treatment factors, to economic analyses and communication.

d) Farm considerations – There is need for improved understanding of the development and transmission of AMR on farms, and the potential negative consequences of reduced antimicrobial use.

e) Data – Access to standardised, open access data is needed to further research, but may be hindered by the perceived sensitivity of some data.

Detailed sets of research questions raised follow in Section 3.

As another way of considering needs for more knowledge, participants were also invited to flesh out a relevant Department of Health map of routes to antimicrobial resistance www.gov.uk/publications/antimicrobial-resistance-amr-systems-map . A brief summary of such additions included:

- Wildlife linkages, such as starlings on settling tanks or veterinary treatment of wildlife.
- Companion animals implicated in AMR are often not discussed in sufficient detail.
- Impact of cleaning and disinfection procedures in farms and the development of environmental AMR, spread of AMR by mixing animals within farms or across generations, and market signals from retailers affecting behaviours.
- Animal feed – disposal of waste from feed containing antibiotics.
- Slurry pits - separation of liquids and solids and the impact of different destinations for each e.g. applying waste from anaerobic digesters to land.
- AMR in the environment -link to disposal of parkland waste, e.g. grass and leaves, composted and returned to the land.
- Abattoir and carcase processing with link to contamination from workers and food handlers.
- Existing AMR presence, without causative agent, and its influence on subsequent development of resistance.

3. DETAILED RESEARCH QUESTIONS

a. Sources of AMR

What is the relative contribution of antibiotic use in livestock to the human clinical resistance crisis – will reduction to 50 mg/PCCI in livestock reduce the human resistance crisis to acceptable levels in the medium to long term?

Where is AMR coming from, and what are the relative contributions of different sources? How much is coming from use of antibiotics, biocides and heavy metals? What are the relative contributions of environment, farm livestock, humans, companion animals, wildlife?

What is the problem being addressed? Are we striving for ‘antibiotic free’ products for consumers and does this compromise animal welfare? What is the appropriate balance among food security, human health and environment?

b. Mitigation methods

In the short term - big gains are possible from motivating behavioural change, including better communication, cost incentives, government intervention and policy, and working out how to implement change in livestock production globally.

In the medium term – there is potential from developing technologies to minimise spread of AMR in the environment, including alternatives to antibiotics, remediation and diagnostics for better use.

In the longer term – there would be value in assessing the risks between drivers of AMR leading to guideline limits on substances released into the environment e.g. guidelines for biocides and metals (if these are meaningful).

Better education and raising awareness of the problem is needed. Everyone contributing to AMR should be involved, rather than just punishing and blaming specific groups. It would be valuable to provide evidence for farmers that reducing antibiotic use gives reduced AMR, and demonstrate in the context of their significant community that reduced use has an impact. Raise awareness that agriculture may develop resistance problems in 25-30 years, even if it does not have resistance problems now, unless action is taken. Improve communication across all sectors e.g. vets understood that Colistin was too toxic for human use and therefore it was used widely by vets. Vets were not aware that it had become a medicine of last resort.

Eradicate immune modulating diseases such as BVD, this will reduce use of antibiotics on farms. Develop and share knowledge on how to get all areas of industry to agree on a course of action, such as eradicating a disease.

Implementation of change at a global level could learn from global management of greenhouse gases. It could be possible to devise a metric to measure AMR and achieve global agreements on reduction of AMR. Similar instruments to those used for greenhouse gas emissions could be used e.g. trading schemes, pollution bubbles, cap and trade. Ways of rewarding the lowest cost ‘polluters’ need to be found.

A hierarchy of technical effectiveness of mitigation methods and their relative costs is needed to aid decision-making. Biocide safety evaluation needs to include evaluation of their propensity to stimulate development of AMR. The possibility should be investigated of developing methods of administered antibiotics individually to pigs, as they are for cattle. More control is needed over sewage treatment.

Make a start on remediation technologies to reduce environmental AMR.

Develop rapid diagnostics (to identify disease organism and its susceptibility to specific antibiotics) to make better use of antibiotics we have.

c. Underlying scientific questions

The over-arching theme was to better understand drivers of AMR on farms. Questions raised included:

What are the co-costs/co-benefits of reducing AMR (including on trade flows and ecosystem resilience) and what are the co-costs/benefits of reducing use of antimicrobials (in terms of human health, economic viability, food security, international trade and ecosystem resilience)?

What is the 'natural' level of AMR on farms? What would the microbial composition have looked like before intensive farming? AMR develops in the gut/environment naturally, even when antibiotics, biocides or heavy metals are not used. What is this base level? What happens to the AMR load when antimicrobial use stops (in quantitative terms) at the individual farm level and in the environment? If use of a specific antibiotic class stops, what happens to the genetic context of the AMR genes?

What is driving AMR? Are there non-antibiotic drivers? What role do heavy metals and biocides play in the development and persistence of AMR? What are environmentally relevant concentrations of antibiotics, metals & biocides needed for selection of AMR? What is the relative importance of metals and biocides for AMR selection and maintenance in soil and rivers, animals and humans? How do we reconcile the use of biocides and biosecurity with decreasing antimicrobial use whilst biocide use also potentially contributing to the AMR problem?

What are the other co-associations of genes with AMR genes that lead to maintenance in an organism in specific hosts/environments? What are the roles of co-selection and co-carriage in AMR development? What specific genes can be co-selected and why? What is the role of mobile elements? To what extent does genotype correspond to phenotype? The presence of resistance genes does not equate to expression, so there is a need to monitor expression profiles of resistance genes in the environment.

How much of the causative agent is taken up by the animal?

What is the fate of resistance elements following waste/manure treatment e.g. phage activity in sewage plants/slurry tanks?

What would be the impact of delivering antibiotics via water delivery systems on groundwater quality?

What are the best ways of communicating AMR issues to the public?

d. Farm considerations

The over-arching theme was the need to understand more about the development and transmission of AMR on farms, and the potential negative consequences of reduced antimicrobial use.

What is the cost:benefit of reduced antibiotic use against negative impacts on animal welfare and reduced productivity? What are the cost:benefit in alternative production systems?

What are viable alternatives to using disinfectants on farms and how effective are vaccines at controlling diseases? Do negative impacts of husbandry systems overwhelm vaccine action?

How much heavy metals and biocides are used on farms now?

A detailed research project to examine AMR development and flows on individual farms would help understand the complexity of AMR development and transmission. Specific

types of farms/geographical should be selected to undertake this detailed research, and could include comparison between farms using different amounts of biocides/heavy metals.

Is it possible to remove antibiotics from farm waste and would it reduce AMR development?

e. Data

The overwhelming theme was how can better data be collected in order to use these data as a predictive tool?

There is lack of a unified method of measuring AMR, so results from different sources cannot be compared. Disparate industries currently measure AMR in different ways. Agreement is needed on methods of measurement, so that the processes can be quantified and different information compared. There is lack of clarity on what are the key metrics to measure. A common database recording structure, in a common format and with open access is needed.

There was a desire to have open source data on AMR that can be accessed by the research community. It was recognised, however, that some data may be sensitive and difficult to share, although it is not clear how sensitive data is defined, nor the conditions under which data could be shared.

Ideally, access to data on the following are needed: AMR in healthy animals on farms, data on morbidity and mortality rates, Food Conversion Efficiency, profitability, environmental pollution, trends in resistance types and dysbacteriosis (alteration of microbiota which allow overgrowth e.g. Salmonella).

In order to take global dissemination into account, monitoring and measuring what is coming into the country is needed. However, in the absence of international data and metrics, nobody knows what the optimum level of antibiotic use is globally. Additional community-based data are needed as well as prescription data, impacts on food security and impact of counterfeit medicines. Partnerships with middle-income countries, and among academia, industry and pharma are needed.

4. PRACTICAL ON-FARM PROCEDURES

The group were invited to consider practical on-farm measures and/or management practices - thinking about what measure or practice would potentially have the greatest impact on AMR; what might be in use or in pilot stages now; and what could be implemented relatively easily or even instituted right away?

a. Reducing antimicrobial use on farm

Farmers tend to use antibiotics using the principle of what worked before. If prescribing practices are to be changed, farmers will need evidence that if they change their practices, there won't be adverse consequences. Improved on-farm recording of antibiotic use and disease levels, with a view to reducing use could be a very effective mechanism for reducing

use of antibiotics. Some farms are already doing this, and examples of commercial farms with low levels of antibiotic use could be used as exemplars to the industry.

b. Changing farm management practices

Effective biosecurity measures can be important but they need to form a coherent package, not including conflicting measure, and need to be complied with. Although biosecurity is practised to some extent, gaining behavioural commitment from time poor farmers is challenging, particularly where there is little benefit to individual farmers.

Changes in manure management could be important. Stacking and storing manure for 8 weeks or more, should be effective in reducing AMR but it is not feasible to do in practice. Anaerobic digestion may reduce AMR but evidence is needed that this is the case. One option is to transfer slurry to a central digester, but it is not clear if this would be feasible. Bedding animals using reclaimed manure is possible, but there may be associated risks with AMR development.

Acidification of water for improved gut health is an easy measure to implement on farms and has low cost. This measure is already widely implemented.

A range of health management practices can be adopted, such as vaccination, breeding for disease resistance, and improvement of internal biosecurity e.g. by use of all-in all-out systems where possible. Novel technologies, such as devices to detect air borne substances could prove to be useful in housed animals. It is much more difficult to control the environment in extensive systems of production, but the level of AMR in extensive systems is not clear.

Smart phone apps could be developed to assist farmer decision-making, once there is sufficient available useful knowledge to help management decisions.

c. Industry led eradication programmes

Eliminating endemic diseases would be effective in reducing use of antibiotics, but such programmes are difficult to implement. Some programmes exist but there scope to increase the number of programmes.

d. Rapid diagnostic devices

The availability of rapid diagnostic devices enabling diagnostic testing to be done on site could have a big impact, but devices are difficult to develop. Many people are working on this area. It is critically important that the devices work and reduce the risk of misidentifying disease. Devices to distinguish between viral or bacterial disease, or use for sensitivity testing could also be useful.

5. CONCLUSION

In summary, antimicrobial resistance, livestock and the environment are closely intertwined. The complexity of the processes involved provides a challenging research environment. Without a broad perspective, important factors can be forgotten (such as the potential role of biocides). Without input from relevant practitioners, flows of materials and important practices may not become apparent. Without practical knowledge, inappropriate remedies can be promoted. Farmers are at the sharp end of these issues and need to be engaged with and given credible reasons for changing what they do, recognising their limited labour availability and economic environment.

Drawing on a unique range of perspectives, this workshop identified both key scientific questions that need answering, infrastructures that would greatly help research (such as availability of data), potential trade-offs that need to be evaluated and questions related to social behaviours, understanding which could make a real difference in resolving issues.

Thank you to all the participants who gave so generously of their time and expertise.

Dr Ann Bruce, ESRC-NERC Agri-Food Knowledge Exchange Fellow (ann.bruce@ed.ac.uk), 15th September 2016

Meeting facilitated by Laura Meagher

ANNEX 1

Andrew Singer: Developing a more holistic understanding of AMR for informing Action Plans

The problem with AMR, globally, is the combination of: 1) increased prevalence of antibiotic resistance; 2) rapid spread of AMR due to global travel; 3) antibiotic misuse; and 4) too few new antimicrobials in development.

National, regional and global AMR Action Plans have been drafted to tackle many of these problems. Thorough reviews, such as the O'Neill AMR Reviews, provide a useful overview of these challenges and some mitigation measures.

However, symptomatic of the O'Neill Reviews and all AMR Action Plans is their under appreciation of the role that the environment plays in the selection, spread and transmission of AMR. Discussions of the environment are typically limited to the pharmaceutical manufacturing plants as a source of antibiotics and the role that sewage and farm run-off can play in dissemination of antibiotics. The discussions on these issues are superficial and narrow in scope.

Current AMR Action Plans and the O'Neill Reviews see antibiotics as the only driver of AMR; hence, all mitigating measures are focused solely on reducing their use and release into the environment. This vision of the challenge of AMR is not helpful as it omits other AMR drivers that could be, on their own, more important than antibiotics for selecting, maintaining and spreading AMR in the environment, let alone as a collective group of AMR drivers.

The class of chemicals characterized as biocides are used in all parts of society from home, to hospital to farms and industry. The presence of biocides selects for genes in microorganisms that can protect against their lethal effects. These biocide resistance genes are often the same genes as antibiotic resistance genes (i.e., cross-resistance), or they can be co-located on plasmids, for example, which means when biocides are present the microorganism will also co-select for antibiotic resistance genes (i.e., co-resistance). As a result of co-selection you can still have elevated levels of antibiotic resistance genes in an environment where antibiotics might be sufficiently low to no longer be select for resistant bacteria. This is a very important outcome as it means AMR Action Plans might fail to achieve their goal without a more holistic plan to address all the AMR driving chemicals.

A second class of chemicals that can drive and co-select for antibiotic resistance genes are metals. These genes operate in much the same way as biocide and antibiotic resistance genes. There are numerous sources of metals in our society which make their way into our soils and rivers, such as: industry effluent, WWTP P-dosing, traffic-related emissions, nanoparticles, textiles, mining, food additives in humans and animals, fertilizers, pesticides.

There is a need to focus on all of these AMR driving chemicals when constructing an AMR Action Plan. In the short term it might be prudent to focus on reducing the use of these chemicals and recycling where possible. However, it is possible that these reductions will not be enough to reduce the prevalence of AMR in the environment below critical thresholds. As a result, we need to determine which of these chemical classes are most

important for selecting, maintaining AMR in the environment and focus our efforts on reducing their use and emissions. It is also critical to know what the critical thresholds are for selection in the environment. These are probably our biggest unknowns at the moment. On-going work in my lab are aiming to tackle these key questions.

ANNEX 2

Research questions identified from Webster and Armstrong talks

In *Discussion* following Grace Webster's talk, the following points were made:

- Biosecurity is a challenge on extensive (sheep) farms,
- The speed with which diagnosis is needed from a rapid diagnostic device will depend on the disease. Minutes would be very desirable, but even hours would be a good step forward compared to the 48 hours it takes now.
- Distinguishing between bacteria and viruses is less important as most diseases form a mixed aetiology. Controlling secondary infections is important. Additionally, waiting for animals to get better of their own accord is different to waiting for humans to get better of their own accord, because of the commercial imperative to keep the animals growing fast.
- Is the term 'inappropriate use' an appropriate description? What is inappropriate use? Some might use the term if a whole population is treated because it is not possible to treat a small group, yet on the other hand individual injections are stressful for both animals and animal carers.

Research questions identified by Derek Armstrong included:

- Why antibiotics are used and what is the impact of their use?
- How important are the potential pathways of AMR from livestock to humans? AMR also needs to be considered on an international basis.
- What is the impact on pathogens of feeding antibiotic treated milk to calves?
- How are decisions made as to: when to treat or not to treat animals with antimicrobials? Which antibiotic should be used? How much antibiotic should be used? Which route is best to use? And how long should treatment last?
- If milk is pasteurised, does this eliminate the risk of AMR transmission?
- Does the concurrent use of anti-inflammatories have an impact on AMR?
- What are the risks of AMR developing in the (clean) environment of the udder, vs. the (dirty) environment of the gut?

ANNEX 3 People registered to attend

Derek	Armstrong	AHDB
Matthew	Avison	University of Bristol
Lucy	Beadle	Cranswick
Sam	Beechener	University of Edinburgh
Lisa	Boden	University of Glasgow
Lena	Ciric	UCL (University College London)
Lucy	Coyne	University of Liverpool
Hannah	Donegan	Tesco
Geoffrey	Foster	Veterinary Centre Manager, SAC
Jesus	Gallego	Scottish Government veterinary adviser
David	Gally	The Roslin Institute (University of Edinburgh)
Rachel	Gomes	University of Nottingham
Katherine	Grace	Veterinary Medicines Directorate
Callum	Harris	Veterinary Medicines Directorate
Ed	Haynes	FERA
Jon	Hobman	University of Nottingham
Chris	Hodgson	Rothamsted Research
Penny	Johnston	NFUS
Angela	Lahuerta Marin	Veterinary Research Officer, AFBI
Dominic	Mellor	Veterinary Public Health
Helen	Miller	University of Leeds
Dominic	Moran	SRUC
Grace	Ogorman	NOAH
Lorna	Paton	SRUC
Naheeda	Portocarero	Devenish Nutrition
Richard	Riley	Technical Manager, Cranswick
Katherine	Royse	British Geological Survey
Harriet	Scott	RAFT solutions
Andrew	Singer	Centre for Ecology & Hydrology
Duncan	Sinclair	Waitrose
Nick	Sparks	The Roslin Institute (University of Edinburgh)
Mark	Stevens	The Roslin Institute (University of Edinburgh)
Chris	Teale	APHA
David	Telford	Knowledge Transfer Network (KTN)
Bryn	Tennant	Capital Diagnostics, SAC consulting
Hamish	Waugh	National Sheep Association & farmer
Grace	Webster	Pig vet
Elizabeth	Wellington	The University of Warwick